



Docket No.: PC-0040 CIP

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By: \_\_\_\_\_

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Lal et al.

Title: DIAGNOSTIC MARKER FOR HUMAN CANCERS

Serial No.: 09/877,633

Filing Date:

June 08, 2001

Examiner: Slobodyansky, E.

Group Art Unit:

1652

Box Non-Fee Amendment  
Commissioner for Patents  
Washington, D.C. 20231

**DECLARATION OF DR. TOD BEDILION  
UNDER 37 C.F.R. § 1.132**

I, TOD BEDILION, a citizen of the United States, residing at 132 Winding Way, San Carlos, California, declare that:

1. I was employed by Incyte Genomics, Inc. (hereinafter "Incyte") as a Director of Corporate Development until May 11, 2001. I am currently under contract to be a Consultant to Incyte Genomics, Inc.

2. In 1996, I received a Ph.D. degree in Cell, Molecular and Development Biology from UCLA. I had previously received, in 1988, a B.S. degree in biology from UCLA.

Upon my graduation from UCLA, I became, in April 1996, the first employee of Synteni, Inc. (hereinafter "Synteni"). I was a Research Director at Synteni from April 1996 until Synteni was acquired by Incyte in early 1998.

I understand that Synteni was founded in 1994 by T. Dari Shalon while he was a graduate student at Stanford University. I further understand that Synteni was founded for the purpose of commercially exploiting certain “cDNA microarray” technology that was being worked on at Stanford in the early to mid-1990s. That technology, which I will sometimes refer to herein as the “Stanford-developed cDNA microarray technology”, was the subject of Dr. Shalon’s doctoral thesis at Stanford. I understand and believe that Dr. P.O. Brown was Dr. Shalon’s thesis advisor at Stanford.

During the period beginning before I was employed by Synteni and ending upon its acquisition by Incyte in early 1998, I understand Synteni was the exclusive licensee of the Stanford-developed cDNA microarray technology, subject to any right that the United States government may have with respect to that technology. In early 1998, I understand Incyte acquired rights under the Stanford-developed cDNA microarray technology as part of its acquisition of Synteni.

I understand that at the time of the commencement of my employment at Synteni in April 1996, Synteni's rights with respect to the Stanford-developed cDNA technology included rights under a United States patent application that had been filed June 7, 1995 in the names of Drs. Brown and Shalon and that subsequently issued as United States Patent No. 5,807,522 (the Brown '522 patent). In December 1995, the subject matter of the Brown '522 patent was published based on a PCT patent application that had also been filed in June 1995. The Brown '522 patent (and its corresponding PCT application) describes the use of the Stanford-developed cDNA technology in a number of gene expression monitoring applications, as will be discussed more fully below.

Upon Incyte’s acquisition of Synteni, I became employed by Incyte. From early 1998 until late 1999, I was an Associate Research Director at Incyte. In late 1999, I was promoted to the position of Director, Corporate Development.

I have been aware of the Stanford-developed cDNA microarray technology since shortly before I commenced my employment at Synteni. While I was employed by Synteni, virtually all (if not all) of my work efforts (as well as the work efforts of others employed by Synteni) were directed to the further development and commercial exploitation of that cDNA microarray technology. By the end of 1997, those efforts had progressed to the point that I understand Incyte agreed to pay at least about \$80 million to acquire Synteni. Since I have been employed by Incyte, I have continued to work

on the further development and commercial exploitation of the cDNA microarray technology that was first developed at Stanford in the early to mid-1990s.

3. I have reviewed the specification of a United States patent application that I understand was filed on June 8, 2001 in the names of Lal et al. and was assigned Serial No. 09/877,633 (hereinafter “the Lal ‘633 application”). Furthermore, I understand that this United States patent application was a continuation-in-part application of and claimed priority to United States patent application Serial No. 08/933,750 filed on September 23, 1997 (hereinafter “the Lal ‘750 application”) and that the SEQ ID NO:1-encoding polynucleotides were described in the Lal ‘750 application. (Note that the sequences of SEQ ID NO:1 and SEQ ID NO:2 in the Lal ‘633 application are identical to the sequences referred to as SEQ ID NO:26 and SEQ ID NO:75, respectively, in the Lal ‘750 application.) My remarks herein will therefore be directed to the Lal ‘750 patent application, and September 23, 1997, as the relevant date of filing. In broad overview, the Lal ‘750 specification pertains to certain nucleotide and amino acid sequences and their use in a number of applications, including gene expression monitoring applications that are useful in connection with (a) developing drugs (e.g., the diagnosis of inherited and acquired genetic disorders, expression profiling, toxicology testing, and drug development with respect to cancer), and (b) monitoring the activity of drugs for purposes relating to evaluating their efficacy and toxicity.

4. I understand that (a) the Lal ‘750 application contains claims that are directed to isolated and purified polynucleotides having the sequences disclosed in the Lal ‘633 application as SEQ ID NO:1-encoding polynucleotides, for example SEQ ID NO:2 (hereinafter “the SEQ ID NO:1-encoding polynucleotides”), and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Lal ‘750 application does not disclose a substantial, specific and credible utility for the claimed SEQ ID NO:1-encoding polynucleotides. I further understand that whether or not a patent specification discloses a substantial, specific and credible utility for its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification

pertains at the time of the patent application was filed. In addition, I understand that a substantial, specific and credible utility under the patent laws must be a “real-world” utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Lal '750 application does not disclose a substantial, specific and credible “real-world” utility for the claimed SEQ ID NO:1-encoding polynucleotides, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my considerations, I should determine whether or not a person skilled in the art to which the Lal '750 application pertains on September 23, 1997 would have concluded that the Lal '750 application disclosed, for the benefit of the public, a specific beneficial use of the SEQ ID NO:1-encoding polynucleotides in their then available and disclosed form. I have also been informed that, with respect to the “real-world” utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107 of the Manual of Patent Examining Procedure, under the heading “I. 'Real-World Value' Requirement”:

“Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm.”

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Lal '750 patent application disclosed to a person skilled in the art at the time of its filing a number of substantial, specific and credible real-world utilities for the claimed SEQ ID NO:1-encoding polynucleotides. More specifically, persons skilled in the art on September 23, 1997 would have understood the Lal '750 application to disclose the use of the SEQ ID NO:1-encoding polynucleotides in a number of gene expression monitoring applications that were well-known at that

time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-16 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Lal '750 application, and (b) a number of published articles and patent documents that evidence gene expression monitoring techniques that were well-known before the September 23, 1997 filing date of the Lal '750 application. The published articles and patent documents I considered are:

(a) Schena, M., Shalon, D., Heller, R., Chai, A., Brown, P.O., and Davis, R.W., Parallel human genome analysis: Microarray-based expression monitoring of 1000 genes, Proc. Natl. Acad. Sci. USA, 93, 10614-10619 (1996) (hereinafter "the Schena 1996 article") (copy annexed at Tab A);

(b) Schena, M., Shalon, D., Davis, R.W., Brown, P.O., Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray, Science, 270, 467-470 (1995) (hereinafter "the Schena 1995 article") (copy annexed at Tab B);

(c) Shalon and Brown PCT patent application WO 95/35505 titled "Method and Apparatus For Fabricating Microarrays Of Biological Samples," filed on June 16, 1995, and published on December 28, 1995 (hereinafter "the Shalon PCT application") (copy annexed at Tab C);

(d) Brown and Shalon U.S. Patent No. 5,807,522, corresponding to the Shalon PCT application, titled "Methods For Fabricating Microarrays Of Biological Samples," filed on June 7, 1995 and issued on September 15, 1998 (hereinafter "the Brown '522 patent") (copy annexed at Tab D);

(e) DeRisi, J., Penland, L., and Brown, P.O. (Group 1); Bittner, M.L., Meltzer, P.S., Ray, M., Chen, Y., Su, Y.A., and Trent, J.M. (Group 2), Use of a cDNA microarray to analyse gene expression patterns in human cancer, Nat. Genet., 14(4), 457-460 (1996) (hereinafter "the DeRisi article") (copy annexed at Tab E);

(f) Shalon, D., Smith, S.J., and Brown, P.O., A DNA Microarray System for Analyzing Complex DNA Samples Using Two-color Fluorescent Probe Hybridization, *Genome Res.*, 6(7), 639-645 (1996) (hereinafter “the Shalon article”) (copy annexed at Tab F);

(g) Heller, R.A., Schena, M., Chai A., Shalon, D., Bedilion, T., Gilmore, J., Woolley, D.E., and Davis R.W., Discovery and analysis of inflammatory disease-related genes using cDNA microarrays, *Proc. Natl. Acad. Sci. USA*, 94, 2150-2155 (1997) (hereinafter “the Heller article”)(copy annexed at Tab G);

(h) Sambrook, J., Fritsch, E.F., Maniatis, T., Molecular Cloning, A Laboratory Manual, pages 7.37 and 7.38, Cold Spring Harbor Press (1989) (hereinafter “the Sambrook Manual”) (copy annexed at Tab H); and

(i) Scanlan, M.J., Gordan, J.D., Williamson, B., Stockert, E., Bander, N.H., Jongeneel, V., Gure, A.O., Jager, D., Jager, E., Knuth, A., Chen, Y., Old L.J., Antigens Recognized by Autologous Antiody in Patients with Renal-Cell Carcinoma, *Int. J. Cancer*, 83, 456-464 (1999) (hereinafter “the Scanlan article”) (copy annexed at Tab I).

8. Many of the published articles and patent documents I considered (i.e., at least items (a)-(g) identified in paragraph 7) relate to work done at Stanford University in the early and mid-1990s with respect to the development of cDNA microarrays for use in gene expression monitoring applications under which Synteni became exclusively licensed. As I will discuss, a person skilled in the art who read the Lal ‘750 application on September 23, 1997 would have understood that application to disclose the SEQ ID NO:1-encoding polynucleotides to be useful for a number of gene expression monitoring applications, e.g., as a probe for the expression of that specific polynucleotide in cDNA microarrays of the type first developed at Stanford.

9. Turning more specifically to the Lal ‘750 specification, the SEQ ID NO:2 polynucleotide of the Lal ‘633 specification (referred to as SEQ ID NO:75 in the Lal ‘750 specification) is shown at pp. 155-156 as one of 98 sequences under the heading “Sequence Listing.” The Lal ‘750 specification specifically teaches that the “invention ... provides an isolated and

substantially purified polynucleotide sequence encoding HRM” (Lal ‘750 application at p. 4). It further teaches that (a) the identity of the SEQ ID NO:2 polynucleotide was determined from a lymph node cDNA library (LNODNOT03) derived from a patient with lung cancer (Lal ‘750 application, pp. 31 and 71), (b) the SEQ ID NO:2 polynucleotide encodes for the human regulatory molecule (cancer marker protein) shown as SEQ ID NO:1 (Lal ‘750 application at pp. 31-32), and (c) northern analysis of SEQ ID NO:2 shows its expression predominantly in cDNA libraries associated with secretion, the immune response, and cancer (Lal ‘750 application at p. 32).

The Lal ‘750 application discusses a number of uses of the SEQ ID NO:1-encoding polynucleotides in addition to their use in gene expression monitoring applications. I have not fully evaluated these additional uses in connection with the preparation of this Declaration and do not express any views in this Declaration regarding whether or not the Lal ‘750 specification discloses these additional uses to be substantial, specific and credible real-world utilities of the SEQ ID NO:1-encoding polynucleotides. Consequently, my discussion in this Declaration concerning the Lal ‘750 application focuses on the portions of the application that relate to the use of the SEQ ID NO:1-encoding polynucleotides in gene expression monitoring applications.

10. The Lal ‘750 application discloses that the polynucleotide sequences disclosed therein, including the SEQ ID NO:1-encoding polynucleotides, are useful as probes in microarrays. It further teaches that the microarrays can be used “to monitor the expression level of large numbers of genes simultaneously” for a number of purposes, including “to develop and monitor the activities of therapeutic agents” (Lal ‘750 application at p. 66, line 29 through p. 77, line 4).

In the paragraph immediately following the Lal ‘750 teachings described in the preceding paragraph of this Declaration, the Lal ‘750 application teaches that microarrays can be prepared using the previously mentioned cDNA microarray technology developed at Stanford in the early to mid-1990s. In this connection, the Lal ‘750 application specifically cites to the Schena 1996 article identified in item (a) of paragraph 7 of this Declaration (Lal ‘750 application at p. 67; *supra*, paragraph 7).

The Schena 1996 article is one of a number of documents that were published prior to the September 23, 1997 filing date of the Lal '750 application that describes the use of the Stanford-developed cDNA technology in a wide range of gene expression monitoring applications, including monitoring and analyzing gene expression patterns in human cancer. In view of the Lal '750 application, the Schena 1996 article, and other related pre-September, 1997 publications, persons skilled in the art on September 23, 1997 clearly would have understood the Lal '750 application to disclose the SEQ ID NO:1-encoding polynucleotides to be useful in cDNA microarrays for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 15 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development in September, 1997 (and for many years prior to September, 1997) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identification of undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of the development of any new drug. Accordingly, the teachings in the Lal '750 application, in particular regarding use of the SEQ ID NO:1-encoding polynucleotides in differential gene expression analysis and in the development and the monitoring of the activities of drugs, clearly includes toxicity studies and persons skilled in the art who read the Lal '750 application on September 23, 1997 would have understood that to be so.



11. The Schena 1996 article was not the first publication that described the use of the cDNA microarray technique developed at Stanford to monitor quantitatively gene expression patterns. More than a year earlier (i.e., in October 1995), the Schena 1995 article, titled "Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray", was published (see Tabs A and B).

12. As previously discussed (*supra*, paragraphs 2 and 7), in the mid-1990s patent applications were filed in the names of Drs. Shalon and Brown that described the Stanford-developed cDNA microarray technology. The two patent documents (i.e., the Shalon PCT application and the Brown '522 patent) annexed to this Declaration at Tabs C and D evidence information that was available to the public regarding the Stanford-developed cDNA microarray technology before the September 23, 1997 filing date of the Lal '750 application.

The Shalon PCT patent application, which was published in December 1995, contains virtually the same (if not exactly the same) specification as the Brown '522 patent. Hence, the Brown '522 patent disclosure was, in effect, available to the public as of the December 1995 publication date of the Shalon PCT application (see Tabs C and D). For the sake of convenience, I cite to and discuss the Brown '522 specification below on the understanding that the descriptions in that specification were published as of the December 28, 1995 publication date of the Shalon PCT application.

The Brown '522 patent discusses, in detail, the utility of the Stanford-developed cDNA microarrays in gene expression monitoring applications. For example, in the "Summary Of The Invention" section, the Brown '522 patent teaches (see Tab D, col. 4, line 52-col. 5, line 8):

Also forming part of the invention is a method of detecting differential expression of each of a plurality of genes in a first cell type, with respect to expression of the same genes in a second cell type. In practicing the method, there is first produced fluorescent-labeled cDNAs from mRNAs isolated from two cells types, where the cDNAs from the first and second cell types are labeled with first and second different fluorescent reporters.

A mixture of the labeled cDNAs from the two cell types is added to an array of polynucleotides representing a plurality of known

genes derived from the two cell types, under conditions that result in hybridization of the cDNAs to complementary-sequence polynucleotides in the array. The array is then examined by fluorescence under fluorescence excitation conditions in which (i) polynucleotides in the array that are hybridized predominantly to cDNAs derived from one of the first or second cell types give a distinct first and second fluorescence emission color, respectively, and (ii) polynucleotides in the array that are hybridized to substantially equal numbers of cDNAs derived from the first and second cell types give a distinct combined fluorescence emission color, respectively. The relative expression of known genes in the two cell types can then be determined by the observed fluorescence emission color of each spot.

The Brown '522 patent further teaches that the “[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention” can be used in “numerous” genetic applications, including “monitoring of gene expression” applications (see Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

13. Also pertinent to my considerations underlying this Declaration is the DeRisi article, published in December 1996. The DeRisi article describes the use of the Stanford-developed cDNA microarray technology “to analyze gene expression patterns in human cancer” (see Tab E at, e.g., p. 457). The DeRisi article specifically indicates, consistent with what was apparent to persons skilled in the art in December 1996, that increasing the number of genes on the cDNA microarray permits a “more comprehensive survey of gene expression patterns,” thereby enhancing the ability of the cDNA microarray to provide “new and useful insights into human biology and a deeper understanding of the gene pathways involved in the pathogenesis of cancer and other diseases” (see Tab E at p. 458).

14. Other pre-September, 1997 publications further evidence the utility of the cDNA microarrays first developed at Stanford in a wide range of gene expression monitoring

applications (see, e.g., the Shalon and the Heller articles at Tabs F and G). By no later than the March 1997 publication of the Heller article, these publications showed that employees of Synteni (i.e., James Gilmore and myself) had used the cDNA microarrays in specific gene expression monitoring applications (see Tab G).

The Heller article states that the results reported therein “successfully demonstrate the use of the cDNA microarray system as a general approach for dissecting human diseases” (Tab G at p. 2150). Among other things, the Heller article describes the investigation of “1000 human genes that were randomly selected from a peripheral human blood cell library” and “[t]heir differential and quantitative expression analysis in cells of the joint tissue. . . to demonstrate the utility of the microarray method to analyze complex diseases by their pattern of gene expression” (see Tab G at pp. 2150 *et seq.*).

Much of the work reported on in the Heller article was done in 1996. That article, therefore, evidences how persons skilled in the art were readily able, well prior to September 23, 1997, to make and use cDNA microarrays to achieve highly useful results. For example, as reported in the Heller article, a cDNA microarray that was used in some of the highly successful work reported on therein was made from 1,000 genes randomly selected from a human blood cell library.

15. A person skilled in the art on September 23, 1997, who read the Lal ‘750 application, would understand that application to disclose the SEQ ID NO:1-encoding polynucleotides, for example, SEQ ID NO:2, to be highly useful as probes for the expression of that specific polynucleotide in cDNA microarrays of the type first developed at Stanford. For example, the specification of the Lal ‘750 application would have led a person skilled in the art in September, 1997 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cancer to conclude that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:1-encoding polynucleotides. Persons skilled in the art would appreciate that cDNA microarrays that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the

polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(g) below a number of reasons why a person skilled in the art, who read the Lal '750 specification in September, 1997, would have concluded based on that specification and the state of the art at that time, that the SEQ ID NO:1-encoding polynucleotides would be a highly useful tool for inclusion in cDNA microarrays for evaluating the efficacy and toxicity of proposed drugs for treating cancer, as well as for other evaluations:

(a) The Lal '750 application teaches the SEQ ID NO:1-encoding polynucleotides to be useful as probes in cDNA microarrays of the type first developed at Stanford. It also teaches that such cDNA microarrays are useful in a number of gene expression monitoring applications, including "developing and monitoring the activity of therapeutic agents [i.e., drugs]" (see paragraph 10, *supra*).

(b) By September, 1997, the Stanford-developed cDNA microarray technology was a well known and widely accepted tool for use in a wide range of gene expression monitoring applications. This is evidenced, for example, by numerous publications describing the use of that cDNA technology in gene expression monitoring applications and the fact that, for over a year, the technology had provided the basis for the operations of an up-and-running company (Synteni), with employees, that was created for the purpose of developing and commercially exploiting that technology (see paragraphs 2, 8 and 10-14, *supra*). The fact that Incyte agreed to purchase Synteni in late 1997 for an amount reported to be at least about \$80 million only serves to underscore the substantial practical and commercial significance, in 1997, of the cDNA microarray technology first developed at Stanford (see paragraph 2, *supra*).

(c) The pre-September, 1997 publications regarding the cDNA microarray technology first developed at Stanford that I discuss in this Declaration repeatedly confirm that, consistent with the teachings in the Lal '750 application, cDNA microarrays are highly useful tools for conducting gene expression monitoring applications with respect to the development of drugs and the monitoring of their activity. Among other things, those pre-September, 1997 publications confirmed that cDNA microarrays (i) were useful for monitoring gene expression responses to different drugs (see

paragraph 12, *supra*), (ii) were useful in analyzing gene expression patterns in human cancer, with increasing the number of genes on the cDNA microarray enhancing the ability of the cDNA microarray to provide useful information (see paragraph 13, *supra*), and (iii) were a valuable tool for use as part of a “general approach for dissecting human diseases” and for “analyz[ing] complex diseases by their pattern of gene expression” (see paragraph 14, *supra*).

(d) Based on my own extensive work for a company whose business was the development and commercial exploitation of cDNA microarray technology for more than two years prior to the September, 1997 filing date of the Lal ‘750 application, I have first-hand knowledge concerning the state of the art with respect to making and using cDNA microarrays as of September 23, 1997 (see paragraphs 2 and 14, *supra*). Persons skilled in the art as of that date would have (a) concluded that the Lal ‘750 application disclosed cDNA microarrays containing the SEQ ID NO:1-encoding polynucleotides to be useful, and (b) readily been able to make and use such microarrays with useful results.

(e) The Lal ‘750 specification contains a number of teachings that would lead persons skilled in the art on September 23, 1997 to conclude that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool for gene expression monitoring applications relating to drugs for treating cancer than a cDNA microarray that did not contain the SEQ ID NO:1-encoding polynucleotides. Among other things, the Lal ‘750 specification teaches that the identity of the SEQ ID NO:2 polynucleotide was determined from a lymph node cDNA library (LNODNOT03) derived from a patient with lung cancer (Lal ‘750 application, pp. 31 and 71). Moreover, northern analysis of SEQ ID NO:2 shows its expression predominantly in cDNA libraries associated with secretion, the immune response, and cancer (Lal ‘750 application at p. 32). (See paragraph 9, *supra*).

Moreover, the Lal ‘633 specification teaches that the cancer marker protein having the amino acid sequence of SEQ ID NO:1 shares homology with known tumor antigens. In particular, SEQ ID NO:1 has 55% identity to the sequence of the NY-REN-2 tumor antigen (GI 5360085). The NY-REN-2 tumor antigen is described in the Scanlan article (See Tab I). Because of the relationship between the cancer marker protein protein of SEQ ID NO:1 and known functional proteins, and

because those known functional proteins are implicated in cancer, persons skilled in the art in September, 1997 would have considered SEQ ID NO:1-encoding polynucleotides to be an important and valuable addition to a cDNA microarray for use in research into cancer.

(f) Persons skilled in the art on September 23, 1997 would have appreciated (i) that the gene expression monitoring results obtained using a cDNA microarray containing a probe to a sequence selected from the group consisting of SEQ ID NO:1-encoding polynucleotides would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the probe described in (i) and from the cDNA microarray as a whole (including all its other individual probes). These kinds of varying results, depending on the identity of the drug being tested, in no way detracts from my conclusion that persons skilled in the art on September 23, 1997, having read the Lal '750 specification, would specifically request that any cDNA microarray that was being used for conducting gene expression monitoring studies on drugs for treating cancer (*e.g.*, a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) contain any one of the SEQ ID NO:1-encoding polynucleotides as a probe. Persons skilled in the art on September 23, 1997 would have wanted their cDNA microarray to have a probe as described in (i) because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to September 23, 1997.

The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 15, and in paragraph 6, *supra*. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Lal '750 application disclosing to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the SEQ ID NO:1-encoding polynucleotides.

16. Also pertinent to my considerations underlying this Declaration is the fact that the Lal '750 disclosure regarding the uses of the SEQ ID NO:2 polynucleotide for gene expression

monitoring applications is not limited to the use of that polynucleotide as a probe in microarrays. For one thing, the Lal '750 disclosure regarding the hybridization technique used in gene expression monitoring applications is broad (Lal '750 application at, e.g., p.9, line 10-15).

In addition, the Lal '750 specification repeatedly teaches that the polynucleotides described therein (including the polynucleotide of SEQ ID NO:2) may desirably be used as probes in any of a number of long established "standard" non-microarray techniques, such as Northern analysis, for conducting gene expression monitoring studies. See, e.g.:

(a) Lal '750 application at p. 14, lines 20-24 (" [N]orthern analysis is indicative of the presence of mRNA encoding HRM in a sample and thereby correlates with expression of the transcript from the polynucleotide encoding the protein");

(b) Lal '750 application at p. 65, lines 5-9 ("The polynucleotide sequences encoding HRM may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; or in dipstick, pin, ELISA assays or microarrays utilizing fluids or tissues from patient biopsies to detect altered HRM expression. Such qualitative or quantitative methods are well known in the art");

(c) Lal '750 application at p. 65, line 22 through p. 66, line 1 ("In order to provide a basis for the diagnosis of disease associated with expression of HRM, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, which encodes HRM, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with those from an experiment where a known amount of a substantially purified polynucleotide is used. Standard values obtained from normal samples may be compared with values obtained from samples from patients who are symptomatic for disease. Deviation between standard and subject values is used to establish the presence of disease"); and

(d) Lal '750 application at p. 73, lines 12-14 ("Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization

of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound (Sambrook et al., supra)”

The “Sambrook et al.” reference cited in item (d) immediately above is a reference that was well known to persons skilled in the art in September, 1997. A copy of pages from that reference manual, which was published in 1989, is annexed to this Declaration at Tab H. The attached pages from the Sambrook manual provide an overview of northern analysis and other membrane-based technologies for conducting gene expression monitoring studies that were known and used by persons skilled in the art for many years prior to the September 23, 1997 filing date of the Lal ‘750 application.

A person skilled in the art on September 23, 1997, who read the Lal ‘750 specification, would have routinely and readily appreciated that the SEQ ID NO:1-encoding polynucleotides disclosed therein would be useful as a probe to conduct gene expression monitoring analyses using northern analysis or any of the other traditional membrane-based gene expression monitoring techniques that were known and in common use many years prior to the filing of the Lal ‘750 application. For example, a person skilled in the art in September, 1997 would have routinely and readily appreciated that the SEQ ID NO:1-encoding polynucleotides would be a useful tool in conducting gene expression analyses, using the northern analysis technique, in furtherance of (a) the development of drugs for the treatment of cancer, and (b) analyses of the efficacy and toxicity of such drugs.



17. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.

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Tod Bedilion

Signed at Redwood City, California

this \_\_\_\_ day of December, 2002